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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,223	12/27/2001	David Botstein	GNE.2930R1C9	7370

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,223	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/17/02, 4/21/03,*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Part III: Detailed Office Action

Claims 22-41 are pending and under consideration.

The claims are drawn to nucleic acids encoding a protein identified as PRO1800.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

IDS:

The information disclosure statement, filed 5/17/2002, has been considered. The BLAST results demonstrate that applicants are aware of nucleic acids with identity/homology to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the Examiner cannot determine if said sequences constitute prior art. It is further noted the information disclosure statement filed 4/29/2003, which provides sequence alignments, provides such alignments to SEQ ID NOs: 23, 8, 12 and 6; it is not clear to the Examiner what the relevance of such to the claims, which are to nucleic acids of SEQ ID NO: 1 or that encode SEQ ID NO: 2. Clarification is requested.

Priority Determination:

The utility for the claimed nucleic acids is based upon Example 16, in which it is shown that the DNA exists in at least 2-fold higher copy amount in 6/9 of tested lung squamous cell carcinoma cell lines. No priority exists for that result in provisional application 60/112851. The earliest disclosure of this result that can be confirmed by the Examiner is in US Application 09/866034, filed 5/25/01. It is suspected that priority may exist in PCT/US99/28634. Applicants are requested to provide a copy of the relevant portion of that application (corresponding to Example 16) in response to this office action to allow a proper priority determination. Accordingly, priority is set at 5/25/01, with possible priority to 12/1/99, pending review of the PCT application.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any

parent application filed prior to the date recited above which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to that date.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-31 and 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid of SEQ ID NO: 1 or fragments of such that are usable as hybridization probes, does not reasonably provide enablement for degenerate variants of such, which might encode a similar protein, nor for nucleic acids 80, 85, 90, or 95% identical to such, nor which encode a protein 80, 85, 90, or 95% identical to the protein of SEQ ID NO: 1, nor nucleic acids which hybridize to any of the above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to isolated nucleic acids having at least 80% identity to a SEQ ID NO: 1 or that encode the protein of SEQ ID NO: 2 with or without its signal peptide, or which encode the extracellular domain of SEQ ID NO: 2 with or without its signal peptide, or nucleic acids at least 80% identical to such encoding nucleic acids. Dependent claims are directed to vectors and host cells comprising the isolated nucleic acids. The specification contains numerous asserted utilities including use as hybridization probes, in chromosome and gene mapping, in the generation of anti-sense RNA and DNA, to identify molecules that bind to PRO

(including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. None of these asserted utilities is specific for the disclosed PRO1800 nucleic acids or protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO18004.

Because the claimed nucleic acids are described at least in part in terms of the protein that might be encoded, the scope of the protein itself must be considered: The specification teaches that PRO1800 has (unspecified) homology to Hep27, which Hep27 is a member of the short chain alcohol dehydrogenase protein family (page 2). At page 70, the specification states that PRO1800 is a "newly identified Hep27 homolog, and possesses activity typical of that protein", however no activity is known or disclosed for Hep27. The structure of the putative PRO1800 peptide is discussed at page 103 of the specification. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1800. Without any information as to the specific properties of PRO1800, the mere identification of such as belonging to the "short chain alcohol dehydrogenase protein family" is not sufficient to impart any particular utility to the claimed polypeptides. The structure of the putative PRO1800 peptide is not discussed in the specification; there is no disclosure that the protein is expected to be a transmembrane protein, nor of any extracellular domain.

The sole disclosed utility that is determined by the Examiner to meet the requirements of 35 U.S.C. §101 is as a probe, as the specification discloses at pages 111-117 that the nucleic acid of SEQ ID NO: 1 is amplified in a significant number of lung squamous cell carcinoma samples. However, the use as a nucleic acid hybridization probe does not confer utility to the protein encoded by the nucleic acid, nor to nucleic acids that vary from the one originally identified. As such, nucleic acids that are claimed by what they encode, rather than the structure of the nucleic acid itself, are not enabled in a manner commensurate in scope with the claims, as only one of the innumerable embodiments is actually the sequence of SEQ ID NO: 1.

With respect to uses of the claimed nucleic acids for purposes other than encoding protein, e.g. diagnostic applications or hybridization use, enablement is commensurate in scope only with claims to nucleic acids that are fragments of SEQ ID NO:1, said fragments of sufficient length to be used as hybridization probes or primers. The specification discloses that SEQ ID NO: 1 is found in increased copy number (apparently 2 fold) in numerous lung squamous cell carcinoma samples. However, enablement is *not* commensurate in scope with fragments of nucleic acids that differ from SEQ ID NO: 1 due to codon degeneracy, as it is not recognized in the art to use such sequences that are degenerate for such detection or synthesis, and the specification provides no guidance as to how or why to make such degenerate primers. The specification also is not enabling of the breadth of claims to nucleic acid molecules that hybridize to the disclosed sequences.

Similarly, the breadth of the language of the claims for any DNA molecule that hybridizes, even under high stringency conditions, is not commensurate in scope with the enablement provided by the specification. First of all, it is pointed out that the term "hybridize" or "hybridization" generically refers to a process in which a strand of nucleic acid joins or matches up with a complementary strand through the process of base pairing, wherein the process is basically used to locate or identify DNAs encoding specific proteins. It is well established in the art that 15-20 bases have been considered sufficient to achieve this process. The breadth of the claims includes nucleic acids of as little as 10 nucleotides. With these points in mind, it is the Examiners position that giving the Claims their broadest reasonable interpretation, this language reads on an infinite number of possible DNA sequences for which there is not sufficient enablement.

The examples provided in the specification do not provide a representative number of different DNA sequences that would enable a representative number of the above discussed DNA sequences with assurances that they possess or encode proteins having the desired activity, or alternatively can be used as probes or primers for the purpose of amplifying or detecting the PRO1800 gene. The mere recitation of this term, and the definitions provided do not serve as sufficient guidance to enable the breadth of the Claims for the various DNA sequences claimed. See Ex parte Forman, 230 USPQ 546. Since the first paragraph of the statute under 35 U.S.C. 112 requires that there must be an enabling disclosure to support the breadth of the Claims, a

review of the specification confirms that the scope of the various DNA sequences that are discussed above have not been enabled. There is but a single nucleic acid disclosed with reference to PRO1800, SEQ ID NO:1. In the absence of sufficient guidance, it would require undue experimentation to enable a commensurate number of the sequences that are encompassed by the Claims.

Claims 22-27, 30-31, and 35-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence, or that merely hybridize to a disclosed sequence. The claims do not require that the claimed polynucleotide encode a particular protein, nor that any protein encoded thereby possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polynucleotides that are defined only by sequence identity. Further, numerous of the claims define such in relation to the 'extracellular domain' of the protein, for which there is no description in the specification.

The specification teaches that PRO1800 has (unspecified) homology to) homology to Hep27, which Hep27 is a member of the short chain alcohol dehydrogenase protein family (page 2). At page 70, the specification states that PRO1800 is a "newly identified Hep27 homolog, and possesses activity typical of that protein", however no activity is known or disclosed for Hep27. The structure of the putative PRO1800 peptide is discussed at page 103 of the specification, but includes disclosure that the protein is expected to be a transmembrane protein, nor disclosure of an extracellular domain. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1800.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, nucleic acids comprising the sequence set forth in SEQ ID NO:1, with or without the portion encoding the signal sequence, or fragments thereof sufficiently long to be used as hybridization probes but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear

that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Deposit Requirement:

Claims 22-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R.§§1.801-1.809). Examiner acknowledges the deposit of organisms under accession number ATCC 203538 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement(see specification, page 130). However, in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at least 30 years *and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository*. See 37 C.F.R.§1.806.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims that recite "the extracellular domain" of the protein are indefinite as no extracellular domain has been described. Therefore, the metes and bounds of the claims cannot be determined. For example, see Claim 22, parts (c) and (d). Further, if the protein had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal

sequence" (claim 22, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Claims that recite that the claimed nucleic acid "hybridizes to" another sequence, such as claim 35, are indefinite as there is no limiting definition of such in the specification, and the metes and bounds of that which will hybridize are dependent upon the conditions under which the hybridization is performed. As the metes and bounds of what will hybridize to a given sequence are entirely dependent upon the conditions of hybridization and washing, the metes and bounds of the claims cannot be determined. With respect to claim 53, although the further limitation that the hybridization conditions are "stringent" is introduced, the term "stringent conditions" is also a relative term, and the metes and bounds of the claim cannot be determined.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The effective priority date is 5/25/2001.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-37 are rejected under 35 U.S.C. 102(b) as being anticipated by F. Gabrielli et al., Eur. J. Biochem 232:473, 1995, cited by applicants.

Gabrielli et al. teach a protein 62% identical to SEQ ID NO: 2, the nucleic acid encoding such having sufficient regions of identity to SEQ ID NO: 1 such as to hybridize to such, even under "stringent" conditions. Accordingly, the claims are anticipated by Gabrielli et al.

Claims 22-32 and 34-41 are rejected under 35 U.S.C. 102(b) as being anticipated by DE 198 18 620 (Rosenthal et al.), cited by applicants.

Rosenthal et al. disclose a nucleic acid, SEQ ID NO: 10, which is 100% identical to SEQ ID NO: 1 of the instant application, with the exception of nine nucleotides at the amino terminus of SEQ ID NO: 1. A translation of pages 1-5 and 132-133 of Rosenthal is provided, in which it is disclosed that the invention includes vectors and host cells, and fusion constructs (see pages 3-4 of translation). The person of ordinary skill in the art would recognize that numerous of the vectors listed at page 3 of the translation are specific to *E. coli*. Accordingly, the claims are anticipated.

Claims 22-32 and 34-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank locus AF044127, disclosed 5/27/1999. The clone is identical to nucleotides 11-terminus of SEQ ID NO: 1 of the instant application. It is disclosed as having been cloned in an M13 phage expression library, thus being an expression vector, and utilizing *E. coli* as a host cell strain. Accordingly, the claims are anticipated.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz. ***Effective 1/21/2004, Dr. Kunz' telephone number is 571-272-0887.***

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner